

## Epithelial Ovarian Tumors of Borderline Malignancy

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Received April 10, 1990

Between January 1975 and January 1987, 80 patients underwent primary surgery at Brigham and Women's Hospital for epithelial ovarian tumors of borderline malignancy. Surgical staging revealed 52 (65%) patients with stage IA, 2 (2.5%) with stage IB, 10 (12.5%) with stage IC, 4 (5%) with stage II, 11 (13.8%) with stage III, and 1 (1.2%) with stage IV. All 37 patients with mucinous tumors had stage I disease, whereas 13 (33%) of 39 patients with serous tumors had stage II-IV disease. The mean sizes of mucinous and serous ovarian tumors were 18.7 and 10 cm, respectively. At initial surgery, 48 (60%) patients had a total abdominal hysterectomy with bilateral salpingo-oophorectomy and 16 (20%) had an oophorectomy. Sixteen (20%) patients underwent cystectomy, 6 (37.5%) of whom subsequently had an oophorectomy. All 10 patients treated by cystectomy alone have remained disease free. CA-125 levels were normal in 5 patients with stage I disease, but were elevated in 6 of 8 patients with more advanced tumors. Current disease status was determined in 72 patients (90%); 69 (95.8%) are alive and disease free, 1 (1.4%) patient is alive with tumor, and 2 (2.8%) patients died, free of disease. © 1990 Academic Press, Inc.

### INTRODUCTION

Epithelial ovarian tumors of borderline malignancy were first identified as a separate clinical and pathologic entity by Taylor in 1929 [1]. Subsequently, many authors have reported that this type of tumor has a much more favorable prognosis than invasive ovarian carcinoma [2-12]. The recurrence rate for borderline tumors ranges from 10 to 30%, occurring as late as 10 or more years after presentation [2].

In 1961 the International Federation of Gynecology and Obstetrics (FIGO) first recognized a subtype of ovarian cystadenoma, different from either the benign or malignant types. These borderline tumors have been char-

acterized as neoplasms with no invasion of ovarian stroma, but maintaining a greater degree of cellular proliferation than benign cystadenomas [13-17].

Several recent studies have evaluated the role of ovarian conservation in the management of borderline tumors [9-12,18-20]. Tazelaar *et al.* reported that 20% of patients with stage IA borderline ovarian tumors treated with less than a hysterectomy and bilateral salpingo-oophorectomy recurred after a mean follow-up of 89 months. However, all patients in their study remained alive and free of disease, including those who developed recurrent neoplasia [19].

The role of postoperative adjuvant chemotherapy remains controversial in patients with ovarian tumors of borderline malignancy [8-12,21-23]. Fort *et al.* reported that chemotherapy may eradicate residual disease in patients with epithelial ovarian tumors of borderline malignancy [23]. However, the impact of chemotherapy on survival is yet to be fully elucidated.

The current study reviews the recent experience of the Brigham and Women's Hospital with 80 patients with borderline ovarian tumors. This investigation was undertaken to provide further information concerning the presentation, natural history, and clinical outcome in patients with this disease process.

### METHODS

The diagnosis of epithelial ovarian tumor of borderline malignancy was based on a thorough review of all pathology specimens by two of the authors (J.M.L. and D.L.Y.). Pathologic review included evaluation of tumor cell type, size of tumor, and extent of disease. One block of tissue was examined for each 1 cm of the tumor's maximal dimension in all cases. Standard histopathologic criteria were used for the diagnosis of all tumor types

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TABLE 1  
Analysis of Tumor Type

Tumor type	Number of patients	%
Serous	39	48.7
Mucinous	37	46.3
Surface	3	3.7
Mixed	1	1.3

[13-17]. Mucinous tumors with epithelial stratification exceeding three cell layers were diagnosed as carcinoma and excluded from this series [5]. Medical records were reviewed in all 80 patients to determine age at diagnosis, gravidity, menopausal status, stage of disease, sites of spread, presence of ascites, size of tumor, operative procedure, postoperative therapy, CA-125 level, and current disease status.

## RESULTS

Eighty patients underwent primary surgery for epithelial ovarian tumors of borderline malignancy at the Brigham and Women's Hospital. The patients' ages ranged from 17 to 77 years with a mean age of 39.0 years and median age of 36.5 years. Table 1 reviews the analysis of tumor type: 39 (48.7%) patients had serous cell type, 37 (46.3%) patients had mucinous cell type, 3 (3.7%) patients had serous surface type, and 1 (1.3%) patient had mixed histology.

All patients were classified according to the new FIGO staging system (Table 2). Stage I, II, III, and IV disease was diagnosed in 80, 5, 13.8, and 1.2% of patients, respectively.

The primary ovarian tumor ranged from 1 to 42 cm, with a mean size of 13.9 cm. Mucinous tumors were significantly larger than serous tumors. While the mean diameter of mucinous tumors was 18.7 cm, the mean diameter of serous tumors was 10.0 cm ( $P < 0.01$ ; two-sample  $t$  test).

TABLE 2  
FIGO Stage

Stage	Number of patients	%
IA	52	65.0
IB	2	2.5
IC	10	12.5
IIA	0	
IIB	1	1.3
IIC	3	3.7
III	11	13.8
IV	1	1.2

TABLE 3  
Tumor Type by Stage

Tumor type	Stage			
	I	II	III	IV
Mucinous	37	0	0	0
Serous	26	4	9	0
Mixed	1	0	0	0
Serous surface	0	0	2	1

Although the mean diameter of mucinous tumors was larger than that of serous tumors, all 37 patients with mucinous tumors had stage I disease. In contrast 13 (33%) of 39 patients with serous tumors had greater than stage I disease. Table 3 compares tumor type by stage. Table 4 reviews all stage I tumors by cell type. Serous tumors were of a higher stage, even among patients with stage I disease. While 35 (94.6%) of 37 stage I mucinous tumors were stage IA, only 16 (61.5%) of 26 patients with stage I serous tumors were stage IA, and 9 (34.6%) were stage IC disease.

Preoperative CA-125 levels were obtained on 13 patients. While all 5 patients with stage I disease had normal CA-125 levels, 6 (75%) of 8 patients with more advanced disease had elevated CA-125 values. However, histology was a confounding factor. All but one patient with stage I disease had mucinous tumors and all but one patient with advanced-stage disease had serous tumors. Thus an elevated preoperative CA-125 level was found in patients with advanced serous tumors.

Table 5 compares the type of surgery performed with the stage of disease. Forty-eight (60%) patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, while 32 (40%) patients were managed conservatively, defined as preservation of some ovarian tissue. Conservation of ovarian tissue was not influenced by the tumor cell type. Eighteen (48.6%) of thirty-seven patients with mucinous tumors and 15 (38.5%) of 39 patients with serous tumors had some ovarian tissue remaining at the completion of surgery. Follow-up is available in 30 (93.8%) of the 32 patients managed conservatively and all are alive and disease free with no further therapy. The two patients with greater

TABLE 4  
Tumor Type in Stage I Disease

Tumor type	Stage		
	IA	IB	IC
Mucinous	35	1	1
Serous	16	1	9

TABLE 5  
Stage by Type of Surgery

Type of surgery	Stage			
	I	II	III	IV
Nonconservative	34	4	9	1
Conservative	30	0	2	0

than stage I disease, who were managed conservatively, are also clinically free of tumor with no further therapy.

Sixteen patients with stage I disease had cystectomy as their primary surgery and six (37.5%) of these patients subsequently underwent oophorectomy. The subsequent oophorectomy tissue revealed tumor in only one (16.7%) of six patients. All ten patients treated with primary cystectomy alone have remained clinically free of disease with no further therapy.

Fourteen (87.5%) of sixteen patients with greater than stage I disease did not receive any postoperative chemotherapy or radiation therapy. Thirteen of these patients remain clinically free of disease with a mean follow-up of 3.7 years (range 1.9–10.8 years). One patient with stage III serous tumor received radiation and chemotherapy for tumor recurrence 7 months following total abdominal hysterectomy and bilateral salpingo-oophorectomy. She is presently alive with disease.

Nineteen patients underwent a pelvic or paraaortic lymphadenectomy at the time of the initial surgery. Three (15%) of these patients had metastatic ovarian tumor of borderline malignancy in the lymph nodes. None of these three patients received further therapy and all remain clinically free of disease at 1.9, 5.8, and 10.8 years of follow-up.

Postoperative therapy was administered to four (5%) patients in this series. One patient with stage IC disease received intraperitoneal  $^{32}\text{P}$  and is alive and disease free. Two patients with stage III disease received systemic chemotherapy and are both alive and disease free. The one patient with stage III serous tumor, previously described, received both radiation and chemotherapy.

Nine (75%) of twelve patients with stage III or IV disease had no residual tumor at the completion of their primary surgery. The three patients with residual tumor underwent hysterectomy with bilateral salpingo-oophorectomy and no further therapy. All three patients remain disease free at 2 to 11 years of follow-up (mean = 5.0 years).

Follow-up was available in 76 patients (95%) with a mean follow-up of 4.1 years. Disease status as of January 1988 was determined in 72 patients (90%). Sixty-nine (95.8%) patients are alive and disease free, one (1.4%) patient is alive with tumor, and two (2.8%) patients died

from other causes free of disease. No patient in our study died of disease. The one patient alive with disease had a stage III serous tumor and underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Both patients who died from other causes had serous tumors. The length of follow-up did not vary according to histologic type of tumor.

## DISCUSSION

Serous and mucinous tumors were the most common cell types. Mucinous tumors were significantly larger than serous tumors, 18.7 cm compared to 10.0 cm ( $P < 0.01$ ). While 13 of 39 (33%) patients with serous tumors presented with disease greater than stage I, all 37 patients with mucinous tumors had stage I disease. Even among patients with stage I disease, serous tumors were more commonly stage IC (34.6%). While 35 patients (94.6%) with mucinous tumors were stage IA, only 16 of 26 (61.5%) patients with stage I serous tumors had stage IA disease.

While the mean age of occurrence for invasive ovarian carcinoma is 52.0 years, the mean age of occurrence for ovarian tumors of borderline malignancy is much younger [2]. The retention of reproductive potential is therefore a concern to many patients with borderline tumors. Lim-Tan and other investigators have concluded that ovarian cystectomy may be adequate therapy in some circumstances [18–20]. Thirty-two patients in this series were managed conservatively, with preservation of some ovarian tissue, and all are clinically free of disease. In particular, 10 patients with stage I disease were treated with cystectomy alone and have remained free of disease. None of our patients died with borderline tumor and only one patient is alive with tumor. The mean follow-up in this study was 4.1 years. However, the long-term outlook in patients with epithelial tumors of borderline malignancy can only be appropriately evaluated with 10 to 20 years of follow-up [2].

The postoperative management of patients with advanced-stage ovarian borderline tumor continues to be controversial. In this series, 13 of the 14 patients with greater than stage I disease, who did not receive postoperative therapy, are clinically free of tumor with a mean follow-up of 3.7 years. One patient developed tumor recurrence 7 months postoperatively and is presently alive with disease following chemotherapy and radiation therapy.

Fort *et al.* reported favorable results in patients with residual disease who received postoperative chemotherapy [23]. Three patients in our series with residual disease received no postoperative therapy and are alive and free of disease with 2 to 11 years of follow-up. Patients with advanced-stage disease may have a favorable out-

look even in the absence of postoperative irradiation and chemotherapy. Studies investigating the value of postoperative therapy in patients with epithelial ovarian tumors of borderline malignancy should consider including a no-treatment group.

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